BRITISH MEDICAL BULLETIN

May 1943 Vol. 1. No. 3

The object of this Bulletin is to provide a guide to medical science and thought in Britain, and it consists mainly of summaries of a representative selection of British papers on subjects of medical interest. Any material appearing in the Bulletin may be published without fee, but acknowledgment of the source, by addition of the initial letters BMB followed by the serial numbers of the items selected, would be appreciated. The Bulletin is not distributed generally to the medical profession.

LOCAL CHEMOTHERAPY NUMBER

SPECIAL CONTRIBUTION

RECENT ADVANCES IN THE ANTISEPTIC TREATMENT OF WOUNDS
by Professor L. P. Garrod ... 26

Chemistry and Physics of Antiseptics ... 28
Absorption from Locally Applied Sulphonamides ... 28
Sulphonamides in Experimental Wounds ... 29
Sulphonamides in Wounds and Burns ... 30
Local Chemotherapy in Experimental Eye Lesions ... 30
Sterilization of Sulphanilamide Powder ... 30
Epileptogenic Property of Sulphathiazole ... 31
Present Status of Flavines as Antiseptics ... 31
Proflavine Powder in Wound Therapy ... 32
Propamidine—A New Local Chemotherapeutic ... 32
Promin in Superficial Tuberculous Lesions ... 34

AVIATION MEDICINE

The Eustachian Tube at increasing Atmospheric Pressures ... 34

INDUSTRIAL MEDICINE

Treatment of the Injured Workman ... 35
An Industrial Lung Disease ... 35

UROLOGY

Non-Gonococcal Urethritis ... 36

LIBRARY
MEDICAL FACULTY,
McGILL
UNIVERSITY

SPECIAL CONTRIBUTION

RECENT ADVANCES IN THE ANTISEPTIC TREATMENT OF WOUNDS

by LAWRENCE P. GARROD, M.D., F.R.C.P.

Bacteriologist to St. Bartholomew's Hospital
Professor of Bacteriology in the University of London

The immense achievements of systemic chemotherapy almost overshadow all other forms of medical progress in the past few years. Yet it will not have escaped the notice of any acute observer that a similar revolution is now taking place in the sphere of local chemotherapy. Antiseptics have been out of fashion since the last war, when they were generally considered to have failed. The orthodox attitude to them has been that they do more harm to tissues than to bacteria, and many surgeons believed that they could neither prevent infection in a wound nor cure it: indeed, in view of this widely held belief it is surprising that antiseptics have been so generally used. Recent observations, of which the following is an account, have rendered this attitude untenable, and there is a prospect that local chemotherapy will improve to the same extent as systemic.

Local Sulphonamide Treatment

For five years after the introduction of the sulphonamides the nature of their action was unknown. German and French authors, including Domagk (1937) himself, hotly denied that they had any useful direct action on bacteria at all, and had this belief not been overthrown there would have been no inducement even to attempt their local application. We owe our present knowledge on this fundamental question to Fildes (1940) and Woods (1940), who showed that the action of sulphanilamide on hæmolytic streptococci is to prevent the utilisation of para-aminobenzoic acid, a previously unrecognised essential growth factor, and that the action of mercury perchloride on bacteria is of exactly the same nature. That this type of reaction wholly explains the action of sulphonamide compounds generally in all bacterial infections is beyond doubt: it is only necessary that there should be a certain excess of the drug over the amount available of the substance essential for growth, and bacterial growth will cease. Since the concentration of the drug attainable by local application is much greater than that produced in the tissues by systemic administration, the former method should succeed. That it does so is now a matter of general experience.

There are records of several earlier attempts to apply sulphanilamide locally, but the first systematic study of its action in wounds was made by Jensen, Johnsrud & Nelson (1939) who, by introducing quantities up to 15 g. into compound fracture wounds, greatly reduced the frequency of infection in them. To trace the development of this form of treatment since it was given a rational basis by the work of Fildes is unnecessary: it is now common practice, and has been found useful in the peritoneum, nose, ear and elsewhere, as well as in wounds. Preventive treatment, as would be expected, is much more successful than curative, and the conditions against which the safeguard afforded is surest are hæmolytic streptococcal infection and gas gangrene. Hawking's (1941) study of prophylactic effect in experimental gas gangrene gives valuable data on the persistence of the powder in the wound and the concentration attained, both of which depend on the solubility of the drug:

	Concentration in wound fluid	*Persistence*
Sulphanilamide	. 1500 mg. per 100 cm.³	less than 1 day
Sulphathiazole	. 104 „ „ „ „	5–6 days
Sulphapyridine	. 42 „ „ „ „	7–10 days

Of these three compounds, sulphathiazole best combines adequate dissolved concentration with duration of effect. It is this persistent action, achieved by the use of a slowly dissolving solid, which secures effective antisepsis.

The success of this treatment has brought about a complete *volte-face* in the surgical attitude to antiseptics generally: scepticism has given place to receptivity, and where one method has succeeded, others both old and new are now given a fair trial.

Proflavine

Among antiseptics available as long ago as the last war, acridine compounds had a unique claim to consideration as wound prophylactics. Not only did they combine a powerful though slow action on bacteria with freedom from any gross toxicity to tissues, but they stood alone in having been shown capable of destroying bacteria in experimental wounds and thus preventing infection. The recent revival of interest in these compounds was assisted by Russell & Falconer's (1940-41) observation that a buffered isotonic solution of proflavine was no more damaging to the surface of the exposed brain than normal saline, whereas other antiseptics applied in the same way caused a severe hæmorrhagic necrosis. Proflavine was included in Hawking's (1941) study, already quoted, of the prophylaxis of experimental gas gangrene, and appears to have been at least as effective as sulphonamides. In the similar experiments of McIntosh & Selbie (1942) proflavine was distinctly more effective than sulphanilamide in preventing the development of *Cl. welchii* infections in mice. Although these recent studies have been concerned only with anærobes, proflavine is equally effective against pyogenic cocci, and there is no doubt that its introduction into a recent wound should be an efficient method of preventing infection generally.

Clinical evidence of its usefulness has been obtained not by prophylactic use but in the much more difficult sphere of treatment. Mitchell & Buttle (1942) [*see BMB* 57] report that the introduction of from 0·5 to 2 g. proflavine powder into intractably suppurating gunshot wounds is often followed by an abrupt cessation of the purulent discharge and rapid healing. Many of their 80 cases had previously had full courses of systemic or local sulphonamide treatment without benefit. It may well be asked why their sensational success should have been achieved with a class of antiseptic which failed to achieve any such striking effect in similar cases during the last war. There are two answers to this question, one of which is the choice of proflavine: the marked superiority of this compound over acriflavine was first emphasised by Albert, Francis, Garrod & Linnell (1938), and strikingly illustrated in the experiments of Russell & Falconer (1940) already quoted. The future of antiseptic treatment with acridine compounds lies with proflavine (2:8 diaminoacridine) and possibly 2:7 diaminoacridine (Albert, Francis, Garrod & Linnell, 1938) and 5 aminoacridine (Rubbo, Albert & Maxwell, 1942): the two latter, which have emerged from the extensive and outstanding work of Albert on the acridines as the most promising among his new compounds, have so far not received adequate clinical trial. The second reason for this success appears certainly to be the method of application. Flavines have never before been used in solid form, and by copying the technique of local sulphonamide treatment, a degree of penetration and persistence has been achieved which is unattainable in other ways. This method deserves general attention and trial.

Propamidine

Propamidine (4:4′ diamidinodiphenoxypropane dihydrochloride) is one of a series of aromatic diamidines recently introduced for the treatment of trypanosomiasis and other protozoal infections. That they also have a powerful action on bacteria was demonstrated by Fuller (1942), who tested a large number of these compounds on many bacterial species. Even the best of them have apparently no systemic effect on bacterial infections, but the local application of propamidine has given excellent results. The rationale of this treatment is explained by Thrower & Valentine (1943) and three succeeding papers in the same journal [*see BMB* 58] describe its clinical effects. Propamidine is applied to wounds in a concentration of 0·1 % in a water-soluble jelly base, the cavity being filled with this or the surface covered with a layer of it, which is then covered with vaseline gauze to prevent escape or evaporation. Application is renewed every two days and the treatment continued for not more than ten. The object is to overcome established sepsis, and this has been achieved when treatment with sulphonamides had previously failed. The scope and effects of propamidine treatment are thus almost identical with those of proflavine in the hands of Mitchell & Buttle (1942), and a deliberate comparison of the two methods would be most instructive. Much remains still to be learned about the action of propamidine on bacteria, its nature, velocity, limitations and variability with species. Existing information on the last point suggests that *Streptococcus pyogenes* is the most susceptible species among common wound invaders: *Staphylococcus aureus* is also susceptible, but less so, while *Proteus* and *Ps. pyocyanea* are resistant.

Biological Antiseptics

This term is applied to antiseptics produced by or extracted from living things, and although it embraces lysozyme and the maggot treatment of wounds, its most important examples are produced by micro-organisms themselves. Bacterial antagonism has been recognised for many years, and is due to the formation by some species of substances destructive to others. One of these is tyrothricin (separable into gramicidin and tyrocidine) extracted by Dubos (Dubos & Hotchkiss, 1941), from *B. brevis*. This substance is highly destructive to gram-positive cocci, and has been successfully used for the local treatment of infections, particularly streptococcal: according to Francis (1942) a sulphonamide-resistant strain responded to treatment with it.

In a class altogether apart stands penicillin. Discovered by Fleming (1929), and re-studied, purified and effectively applied to therapeutics by Florey and his co-workers (Abraham, Chain, Fletcher, Gardner, Heatley, Jennings & Florey, 1941; Florey & Florey, 1943), this astonishing substance presents at the moment the most acute problem in medicine. It is extracted from cultures of a mould, *Penicillium notatum*: the yield is very small, and substantial loss occurs in purification, so that large-scale production involves prohibitive expense. Its exact constitution is unknown and synthesis therefore not in sight. The pure product is non-toxic, exerts a systemic action, and acts on a wide range of bacteria. It is the only known agent which will control staphylococcal septicæmia, and it is effective in infection by sulphonamide-resistant streptococci and pneumococci. That it also has an efficient local action has been shown both by experiment and clinically: in McIntosh & Selbie's (1942) studies it proved superior not only to sulphonamides but to proflavine in preventing experimental gas gangrene in mice. If it ever becomes freely available it will doubtless take an important place as a local antiseptic.

Very many other moulds, particularly of the genera *Penicillium* and *Aspergillus*, have been studied from this standpoint. Raistrick, Smith & Oxford (1941, 1942) have obtained good yields of bactericidal extracts from a number of moulds, and in some cases determined their constitution and even synthesised them. These substances and the mould products obtained by Waksman & Woodruff (1942) and others are without exception less bactericidal and more toxic than penicillin. They are thus unsuitable for systemic use, but may have their uses as a local application.

Methods of Application

Next to the choice of an antiseptic, the method of applying it is the most important factor determining success or failure. Most antiseptics suitable for application to wounds act slowly; they do not kill bacteria outright, but either kill them in periods measured at least in hours, or merely prevent their growth. The antiseptic must therefore be maintained in the wound for hours and even days. This effect is achieved with sulphonamides by applying them as a solid, which undergoes slow solution. The use of proflavine in this form for the first time is unquestionably a major factor in the success achieved by Mitchell & Buttle. It has long been objected against the flavines that their affinity for fabrics is greater than that for tissues: a wet dressing soaked in a flavine solution retains it, and the antiseptic may make no contact at all with some parts of the wound. Irrigation, as usually practised, is only momentary. But to scatter the powder itself in the wound, and allow its slow solution in the wound exudate, is an entirely different matter. The solubility of proflavine is 1 in 300, which by analogy with the behaviour of sulphonamides according to their solubility should secure good persistence. It certainly does remain in a wound for days, perhaps also because it is less readily absorbed than sulphonamides. Acriflavine is probably too soluble for this type of use, besides being less suitable on other grounds. Free solubility used to be considered a good quality in antiseptics: it is no longer so from this standpoint. What is needed for application in powder form is an optimum solubility, which will combine adequate concentration with sufficiently long persistence.

The persistent action of propamidine is secured by filling or covering the wound with a semi-solid preparation of it, and sealing the surface with a waterproof dressing. This is reminiscent of Meleney's technique (Meleney & Harvey, 1939) with zinc peroxide paste, and technique rather than any special virtue in the antiseptic used may well be responsible for his success. Bunyan (1941) secures total and prolonged immersion of the wound in a solution of sodium hypochlorite by enclosing the whole area in the cellulose bag now named after him and running the solution through it. Here again is a method far superior to the Carrel-Dakin method of irrigation used in the last war: the difference is that between a rivulet and a lake. In fact all new methods of treating wound sepsis provide in some way for prolonged and uninterrupted action. We have learned the virtues of antiseptics largely by learning how to use them better.

The Sequence of Discovery

No one before 1935 could have predicted even in his moments of wildest optimism that the control of bacterial infection by chemical means would progress as it has in less than a decade. If he had ventured on such a prophecy, he would certainly have expected local treatment to be perfected first, and systemic—the much more difficult task of attacking bacteria in deeper tissues and even in the blood-stream—to be achieved later. Actually this order has been reversed: systemic sulphonamide treatment had been firmly established for several years before any attempt was made to improve the local treatment of infections. The incentive to re-exploration of this neglected sphere was the success achieved by local application of sulphonamides themselves. In a bare three years since this revival of antiseptic treatment began, three new agents have come into use which will overcome infections in which sulphonamide treatment has failed. What are the relative merits and proper spheres of solid proflavine, propamidine and penicillin, and perhaps of other agents yet to be discovered, can only be decided by much more extensive trials. What is quite certain even now is that wound infections can be prevented by antiseptics, and successfully treated by antiseptics when they occur. Chronic suppuration in wounds is no longer to be tolerated as a sometimes inevitable evil: it calls for active treatment by one of the methods which these recent studies have brought to light.

REFERENCES

Abraham, E. P., Chain, E., Fletcher, C. M., Gardner, A. D., Heatley, N. G., Jennings, M.A., & Florey, H. W. (1941), *Lancet*, **2**, 177

Albert, A., Francis, A. E., Garrod, L. P., & Linnell, W. H. (1938), *Brit. J. exp. Path.*, **19**, 41

Bunyan, J. (1941), *Brit. med. J.*, **2**, 1

Domagk, G. (1937), *Klin. Wschr.*, **16**, 1412

Dubos, R. J., & Hotchkiss, R. D. (1941), *J. exp. Med.*, **73**, 629

Fildes, P. (1940), *Brit. J. exp. Path.*, **21**, 67

Fleming, A. (1929), *Brit. J. exp. Path.*, **10**, 226

Florey, M. E., & Florey, H. W. (1943), *Lancet*, **1**, 387

Francis, A. E. (1942), *Lancet*, **1**, 408

Fuller, A. T. (1942), *Biochem. J.*, **36**, 548

Hawking, F. (1941), *Brit. med. J.*, **1**, 263

Jensen, N. K., Johnsrud, L. W., & Nelson, M. C. (1939), *Surgery*, **6**, 1

McIntosh, J., & Selbie, F. R. (1942), *Lancet*, **2**, 750

Meleney, F. L., & Harvey, H. D. (1939), *Ann. Surg.*, **110**, 1067

Mitchell, G. A. G., & Buttle, G. A. H. (1942), *Lancet*, **2**, 416

Raistrick, H., Smith, G., & Oxford, A. E. (1941, 1942), *Chemistry and Industry*, **60**, 828; **61**, 22, 48

Rubbo, S. D., Albert, A., & Maxwell, M. (1942), *Brit. J. exp. Path.*, **23**, 69

Russell, D. S., & Falconer, M. A. (1940–41), *Brit. J. Surg.*, **28**, 472

Thrower, W. R., & Valentine, F. C. O. (1943), *Lancet*, **1**, 133

Waksman, S. A., & Woodruff, H. B. (1942), *J. Bact.*, **44**, 373

Woods, D. D. (1940), *Brit. J. exp. Path.*, **21**, 74

Dr. L. P. Garrod is Bacteriologist to St. Bartholomew's Hospital and Professor of Bacteriology in the University of London. He has studied many aspects of antiseptic action, including, in addition to the surgical use of antiseptics, their action in selective culture media, assessment by in vitro tests, urinary and intestinal antisepsis, and the bactericidal action of gastric juice.

Professor Garrod has maintained for many years, in opposition to general surgical belief, that the application of suitable antiseptics is capable of preventing wound infections. Since 1931 (St. Bartholomew's Hospital Reports, 64, 85) he has advocated the use of flavines for this purpose. He is author of "Recent Advances in Pathology" (with G. Hadfield); "The Chemotherapy of Bacterial Infections" (Lancet, 1938, 1, 1125, 1178); "The Action of Antiseptics on Wounds" (Lancet, 1940, 1, 798, 845).

CHEMISTRY AND PHYSICS OF ANTISEPTICS IN RELATION TO MODE OF ACTION

by A. Albert, *Lancet*, **2**, 633–636, 28/11/42

In this paper from the Department of Organic Chemistry of the *University of Sydney*, Australia, the author attempts to relate the activity of antiseptics to their physical and chemical properties on the basis of contemporary knowledge of chemical and physical factors in antiseptic action. The following types of antiseptics are distinguished.

1. *Hydrogen and hydroxyl ions as antiseptics*

E.g. the use of ammonium chloride or sodium acid phosphate to render the urine acid and thus inhibit the growth of *Bact. coli.*

2. *Anionic and kationic types of antiseptics*

These were first distinguished by Stearn & Stearn (1924). They are salts in which one ion has much greater molecular weight than the other and they apparently form un-ionised complexes with portions of the bacteria. The *anionic antiseptics* are salts of acids of high molecular weight, *e.g.* common soap, calcium mandelates, acid fuchsin, etc. These react with a protein in the bacteria and there is liberation of the sodium or basic ion which tends to form sodium hydroxide. Hence the reaction proceeds only in the presence of acid, and in practice these antiseptics are useless in infected wounds, moderately useful for skin sterilisation and very useful in the disinfection of the urinary tract, provided that the urine is kept acid.

The *kationic antiseptics* consist of hydrochlorides, etc. of bases of high molecular weight, and they include the basic dyes (brilliant green and crystal violet), the acridine antiseptics and a special group of the colourless higher aliphatic amines (*e.g.* " zephiran ", " CTAB "). The basic part of the antiseptic combines with acidic groups in the bacterium and free acid is liberated. The action of these compounds is more powerful than that of the anionic type since (*a*) bacteria contain more acidic groups than basic groups, and (*b*) more strongly acidic groups (phosphoric) seem to occur in the nuclear apparatus and enzyme systems. Many compounds of this group are active as disinfectants for wounds and for the skin. However, some chemical configurations appear more active than others.

The Stearns postulated that, within limits, the bacteriostatic power ought to increase with increase of the basic strength, because (*a*) stronger bases are more highly ionised, and (*b*) antiseptics derived from strong bases should form complexes with protein which are more resistant to hydrolysis. However, if the base is too strong, it does not produce unionised complexes so easily. The application of this principle to the triphenylmethane dyes (*e.g.* brilliant green) is difficult, as the free bases form tautomeric modifications which complicate measurements of the basicity.

The reason why some kationic antiseptics are ineffective against gram-negative bacteria may be partly explained in terms of basicity, since gram-negative bacteria such as *Bact. coli* possess relatively fewer acidic groups than gram-positive bacteria such as staphylococci. The acridine compounds, on the other hand, form a good example of the influence of basicity. In the series of mono-amino-acridines, investigated by Albert, Goldacre & Rubbo (1941), the strength of the antiseptic action is approximately proportional to the basicity of the compound ; but as postulated by the Stearns, the highly basic compound 2–8 diamino methyl acridine (acriflavine) is no more active than the moderately basic 2–8 diamino acridine (proflavine).

3. *Long-chain polar compounds*

These compounds (*e.g.* " zephiran ") which form a special group of the kationic antiseptics are aliphatic amines with a long side chain of 12–16 carbon atoms. The principal constituent of " zephiran " is lauryl benzyl-dimethyl ammonium chloride. At a surface, the molecules orientate themselves so that the carboxyl or amine group (the head) at one end is in the water, while the lipophilic side chain, or " tail," is repelled from the water. Accordingly these compounds are concentrated at the surface of the water and greatly diminish the surface tension. Such compounds appear to be attracted to the living cell and to become orientated on its surfaces.

4. *Phenols*

The mode of action of these compounds is rather obscure. Phenol itself has little action in lowering surface tension, but its activity in this respect can be greatly increased by inserting a hydrocarbon " tail " (as in " izal " or cresols) or by a combination of halogen and hydrocarbon " tails," *e.g.* chloroxylenol (as in " dettol "). The antiseptic action increases proportionally to the power to diminish surface tension. The author suggests that phenols are concentrated in surface layers and that under these conditions the hydroxy group acts like an acid. If this is true phenols are anionic antiseptics.

The disadvantages of surface-active disinfectants are (*a*) that wastage in wounds is great through adsorption on pus and other debris, and (*b*) that they are always injurious to delicate human tissues.

5. *Other chemical mechanisms*

Formaldehyde acts by combining with the free amino groups of protein ; the halogenating agents, *e.g.* iodine and hypochlorites, act partly by halogenating free amino acids and partly through a direct oxidising action. Some substances, *e.g.* hydrogen peroxide and permanganates, act as oxidising agents.

6. *Sulphonamides*

The mode of action of these compounds has been brilliantly illuminated by Fildes (1940), who postulated that sulphanilamide displaces an essential metabolite—*p*-aminobenzoic acid—from a bacterial enzyme. This mechanism constitutes a refined and specialised chemical attack on a specific functional unit of the bacterium, as opposed to the more generalised chemical activity of other types of antiseptics.

The author concludes by suggesting that the whole subject of the mode of action of antiseptics offers great scope for collaboration between the physical chemist, organic chemist, and bacteriologist.

REFERENCES

Albert, A., Goldacre, R., & Rubbo, S. (1941), *Nature*, **147**, 709

Fildes, P. (1940), *Lancet*, **1**, 955

Stearn, A. E., & Stearn, E. W. (1924), *J. Bact.*, **9**, 491

50

SULPHONAMIDES USED LOCALLY : Their Absorption from Serous Cavities and Wounds in Man

by F. Hawking and A. J. Hunt, *British Medical Journal*, **2**, 604–606, 21/11/42

The sulphonamides are generally accepted to be the most satisfactory compounds for prophylactic local application to contaminated wounds. Owing to the greater concentration achieved at the site of potential infection, they are more effective when inserted into the wound than when given by mouth. The relative value of the different sulphonamide compounds depends partly upon their bacteriostatic activity (sulphathiazole being the most active) and partly on their solubility. The more soluble compounds produce a higher concentration in the fluids of the wound, but they are absorbed more quickly, so that their action is less prolonged.

The authors report from the *National Institute for Medical Research* and *St. Bartholomew's Hospital*, London, a study of the rate of absorption from human operative wounds, but the work was interrupted before completion by the departure of one author for military service. The sulphonamides were inserted as powder (5–10 g.) into the wounds at the end of the operation, which was usually abdominal. The subsequent absorption was followed by taking blood samples at 6, 24 and 48 hours and by measuring the excretion of drug in the urine. The results varied greatly from case to case, and did not depend particularly on the site or nature of the wound. In 11 cases 5 g. of sulphanilamide was inserted. Taken as an average for the group, the daily excretion on the first two days was 1·1 g., after which only small quantities were excreted. The total amount recovered from the urine was 2·5 g., showing that much of the compound is lost in the body. The average blood concentration of free sulphanilamide was 3·2 mg. per 100 $cm.^3$ at 6 hours, 2·7 mg. at 24 hours, and 1·0 mg. at 48 hours. Slightly higher figures were obtained when 7·5–15 g. was inserted. The authors conclude that sulphanilamide remains in the wound in appreciable amounts for not more than 2 days.

When 5–7·5 g. " hypoloid sulphanilamide L.S.F." (15% solution of sulphanilamide lactoside sodium formaldehyde

sulphoxylate) was inserted, most of the excretion occurred within the first 12 hours, indicating that the compound was rapidly removed from the wound and that it is not suitable for local application. Four cases were treated with 4 g. of micro-crystalline sulphadiazine inserted intraperitoneally. Most of the excretion occurred on the second day, but smaller amounts were excreted on the first and third days. The average blood concentration of the free compound was 9 mg. per 100 cm.^{3} at 6 hours, 5 mg. at 24 hours and 3 mg. at 48 hours. The clinical effects of this treatment appeared to be good, allowing for the grave nature of the cases, but in two patients who died from other causes on the eighth and tenth days respectively, small lumps of unabsorbed sulphadiazine were found in the recto-vesical fossa surrounded by adhesions and lymph ; histologically there was little evidence of irritation due to these deposits, but the authors nevertheless consider that sulphadiazine is not the best compound for intraperitoneal use owing to these residues. When a 30% sulphanilamide preparation in an oily base was spread on gauze and packed into wounds of small surface area compared with their volume, the absorption of sulphanilamide was much delayed and was incomplete even after 6 days. Animal experiments have shown, however, that there is a risk when inserting oily preparations into wounds, since most of the oils cause fibroblastic reactions if they become embedded in the tissues (Hawking, 1943) [*see also BMB* **51**].

One of the authors had considerable experience of the use of sulphonamides for wounds caused during air raids. When applied locally they appear clinically to have been of great value in preventing or diminishing the development or spread of infection, and the same has been true of cases in which the peritoneum has been contaminated in various ways. When given by mouth, however, sulphapyridine was not sufficiently active to prevent the development of gas gangrene in a clean wound of the leg two days after radical surgical excision with drainage, during which time full doses of the compound had been given. No general toxic effects after local application were observed in this series.

In view of their own observations and those recorded in the literature the authors recommend sulphanilamide, sulphathiazole, or a mixture of the two, as the most suitable preparations for local application, inserted as a powder or as a fine suspension in saline, *e.g.* micro-crystalline sulphathiazole. Since a case of tetanus recently occurred in London following the intraperitoneal insertion of unsterilised sulphapyridine, it is necessary to sterilise all powder used for this purpose [*see BMB* **54**].

REFERENCE

Hawking, F. (1943), *J. Path. Bact.*, **55**, 41

51

EFFECT OF SULPHONAMIDE PREPARATIONS ON EXPERIMENTAL INFECTED WOUNDS

by F. Hawking, *Lancet*, **2**, 507–510, 31/10/42

During the battles of modern warfare the orthodox surgical treatment of wounds, that is, operative treatment in a properly equipped theatre, is often impractical. Lt.-Col. A. J. Gardham has suggested in a private memorandum to the War Wounds Committee of the *Medical Research Council* that in these circumstances the wounds should be filled with a sulphonamide paste after only a superficial cleansing, and covered with an occlusive dressing which would remain in position for several days.

The present author has investigated this suggestion experimentally in rabbits at the *National Institute for Medical Research* and some aspects of this work have been described elsewhere (Fuller, Hawking & Partridge, 1942 ; Hawking, 1943). Experiments on the absorption of sulphonamides from various oily preparations showed that sulphanilamide is rapidly absorbed *in vitro* from aqueous preparations or from oil-in-water emulsions, but only slowly from water-in-oil emulsions or from oily bases ; however, when tested *in vivo* (by smearing the ointment over a superficial wound in a rabbit) sulphanilamide is absorbed from oily bases almost as rapidly as from watery bases. This failure of oily bases to delay absorption under the conditions *in vivo* is due to the fact that the ointment is present as a thin film, so that the surface is very large compared with its volume. A slower rate of absorption, and thus a longer therapeutic action in the wound, can be obtained best by using one of the less soluble sulphonamides such as sulphathiazole, or the still less soluble sulphapyridine or sulphadiazine (Fuller, Hawking & Partridge, 1942).

Another part of this investigation reported elsewhere in more detail by the present author (Hawking, 1943), was concerned with the histological reactions of the tissues around the wound to the various preparations. When oils are inserted into the tissues they eventually become encapsulated. Vegetable oils cause the least reaction, especially cottonseed oil, which appears to be completely inert, and which lies in the tissues with only a thin wall of fibroblasts around it. Other vegetable oils, such as arachis oil or linseed oil, cause a little more reaction. Mineral oils, *e.g.* paraffin, are surrounded by a curious foam-like tissue containing great numbers of vacuolated phagocytes ; this tissue has often been called a "paraffinoma." Animal oils excite the greatest reaction, especially cod liver oil. After several days in the tissue this oil becomes changed chemically and then causes the appearance of dense collections of giant-cells. Simple aqueous preparations of sulphanilamide or sulphathiazole excite a little inflammation at first but they are afterwards absorbed leaving a minimum of scar tissue.

The author confirmed that these histological reactions to the various preparations occurred in infected wounds, and he recommends that as a rule oils or oily preparations should not be inserted into deep wounds, unless it can be ensured that all the oil can be subsequently removed from the wound. This may be done by applying the oil on gauze, as in the well-known vaseline gauze. From the experimental evidence, it would appear that cottonseed oil is the least harmful and cod liver oil the most harmful.

The experiments on the therapeutic effect of various sulphanilamide preparations which form the main subject of the present paper were made in rabbits wounded in the thigh by inserting scissors through an incision behind the knee and slashing the hamstring muscles as far as the ischium. A small volume of a culture of virulent sulphonamide-sensitive streptococci was inserted ; this contained over 10,000 lethal doses of the organism. Then a standard quantity of the sulphonamide preparation containing 0·6 g. sulphonamide was squeezed into the wound, which was afterwards closed by suturing. The control untreated rabbits all died in 2–3 days with generalised streptococcal septicæmia. The survival of the treated animals was as follows :

(*a*) with a 15% aqueous solution of *sulphanilamide lactoside sodium formaldehyde sulphoxylate* (a soluble preparation issued by Burroughs Wellcome, Ltd.)	0 out of 4
(*b*) with 30% *sulphanilamide* in an aqueous base .	2 out of 10
(*c*) with 30% *sulphanilamide* in oil-in-water emulsion	5 out of 10
(*d*) with 30% *sulphanilamide* in oil	7 out of 10
(*e*) with 20% *sulphathiazole* as a suspension of microcrystals in saline	10 out of 10
(*f*) with 8% *sulphadiazine* as a similar suspension	4 out of 5
(*g*) with *sulphathiazole* injected subcutaneously .	5 out of 5

At the same time, the absorption of sulphonamide from the wound was estimated by measuring the amount excreted in the urine. The order of the preparations arranged according to the slowness of absorption was found to represent also the order of therapeutic effectiveness, and the author concludes that any factor which prolongs the presence of sulphanilamide in a wound thereby increases its therapeutic efficacy. The superiority of the results with sulphathiazole and sulphadiazine may be due partly to their slower activities. In other experiments, treatment was delayed until 6 or 17 hours after the wound had been inflicted and infected. In these cases the therapeutic results were less good.

The effect of these preparations upon the wounds was also studied histologically and the results were similar to those which have been described above. The wounds which had been treated with microcrystalline sulphathiazole or sulphadiazine or with simple aqueous preparations of sulphanilamide were indistinguishable from the control wounds. Those treated with oily preparations showed all the fibroblastic and phagocytic reactions associated with the pure oils.

The author then considers, in the light of this experimental evidence and of such information as is available from the regions of warfare, the original proposal that wounds on the battlefield should be treated by insertion of a sulphona-

mide preparation. Although human wounds which have been excised heal more quickly than those which have received only sulphanilamide powder and dressing, the majority of such wounds do not reach the surgeons until 24 hours or more have elapsed. Under these conditions a simple dressing in the form of a sulphonamide preparation which could be applied by a medical orderly from a collapsible metal tube, would be of value in delaying the development and spread of bacterial infection. The best preparation to use would be the microcrystalline suspension of sulphathiazole (Chambers, Harris, Schumann & Ferguson, 1942). When this is not available, the next best would be a simple aqueous preparation of sulphanilamide, e.g. *sulphanilamide* 30 ; *triethanolamine* 0·33 ; *stearic acid, beeswax* and *wool fat* each 1·4 ; water to 100. This preparation would be less effective therapeutically than some of the others, but it would be cheaper and less harmful histologically. Oily preparations should not be inserted into deep wounds unless incorporated on gauze to ensure complete removal of the oil. For this purpose the author recommends *sulphanilamide* 10–30 ; *cottonseed oil* 30 ; *triethanolamine* 1 : *stearic acid* 2 : *cetyl alcohol* 1·4 ; *chloro-cresol* (as preservative) 0·1 ; water to 100 parts. If cottonseed oil is not available, arachis or castor oil may be substituted.

REFERENCES

Chambers, L. A., Harris, T. N., Schumann, F., & Ferguson, L. K. (1942), *J. amer. med. Ass.*, **119**, 324

Fuller, A. T., Hawking, F., & Partridge, M. W. (1942), *Quart. J. Pharm. and Pharmacol.*, **15**, 127 & 136

Hawking, F. (1943), *J. Path. Bact.*, **55**, 41

52

THE VALUE OF LOCAL CHEMOTHERAPY IN WOUNDS AND BURNS

by D. N. Mathews, *Lancet*, **2**, 271–275, 5/9/42

The writer, who is at present a surgeon in the Royal Air Force, has made a study of the quantitative changes of bacteria present in a series of infected wounds treated with two of the sulphonamide drugs. Twenty neglected wounds and burns were given a daily application of either sulphanilamide or sulphathiazole powder followed by a dry dressing. At each change of dressing a small quantity of the exudate in the wound was removed and diluted in a pipette used for counting red blood corpuscles. Measured quantities of this fluid were grown on agar plates and colony counts were made. Para-amino benzoic acid was added to the culture media in order to neutralise the action of any sulphonamide that might still be present in the exudate (this procedure was adopted in conformity with the findings of Woods, 1940).

In every case there was a great reduction in the number of bacteria per cm.^{3} of exudate during the first few days following the application of the sulphanilamide. This reduction was seen in the numbers of hæmolytic streptococci and also other bacteria, for example, *B. coli*, *B. pyocyaneus*, staphylococci and diphtheroids. The bacteria never disappeared, and after a few days their numbers remained constant. This may be explained by assuming that the organisms became resistant to the action of the sulphonamides. The condition of the wounds rapidly improved and healing progressed.

The concentration of the drugs in the blood and the urine was also estimated by Marshall's colorimetric method. After 1·5 grams of the drug had been applied to a wound the blood concentration rose to a maximum with the first 24 hours and then rapidly declined. A concentration of 1·0 mg. per 100 cm.^{3} of blood was the highest level recorded. In the urine a concentration of up to 24 mg. per 100 cm.^{3} was found, and the author recommends that the urine should be examined for blood and casts in those cases which are subjected to prolonged chemotherapy.

In the light of his own experience and the published reports of other investigators in Britain and the U.S.A. the author concludes that the local application of sulphonamides to wounds is of great prophylactic and therapeutic value.

REFERENCE

Woods, D. D. (1940), *Brit. J. exp. Path.*, **21**, 74

[Another investigation on blood concentrations of sulphanilamide attained after local chemotherapy is reported in *BMB* **21**.]

53

LOCAL CHEMOTHERAPY IN EXPERIMENTAL LESIONS OF THE EYE PRODUCED BY STAPHYLOCOCCUS AUREUS

by J. M. Robson and G. I. Scott, *Lancet*, **1**, 100–103, 23/1/43

Experimental work on the treatment of staphylococcal infections by chemotherapeutic agents has been hampered by the fact that the production of standard staphylococcal lesions suitable for testing the effect of various therapeutic measures has presented considerable difficulty. In the present paper from the Department of Pharmacology, *University of Edinburgh*, the authors describe a method which depends on the production of *staphylococcus aureus* lesions of the cornea in rabbits.

A 24-hour culture of the organism is injected into the cornea, thus producing a small blister under the corneal epithelium. Ulceration of the cornea, usually with hypopyon, results. Equal lesions can be produced in both eyes of any one animal. A technique is thus available for testing the value of chemotherapeutic drugs in the treatment of localised lesions. When the drug is applied locally to one eye in each animal the other untreated eye is used as control, thus largely eliminating the difficulties due to individual variation.

Definite beneficial effects on the development of artificially induced staphylococcal lesions were produced by the repeated local application of (*a*) a crude preparation of penicillin * in solution, and (*b*) 30 % and 10 % solutions of sodium sulphacetamide (albucid soluble). A 15 % solution of solubilised sulphathiazole (sulphathiazole sodium formaldehyde sulphoxylate) was less effective ; tyrothricin and 2·5 % sodium sulphacetamide were of little or no value. In all these experiments treatment was begun an hour after inoculation. When the treatment was begun 24 hours after inoculation little or no benefit was produced by the application either of penicillin or of 10 % sodium sulphacetamide. The application of penicillin eliminated the *staphylococcus aureus* from the flora of the conjunctival sac, but this was not achieved when 10 % sodium sulphacetamide was used. Commenting on the clinical implications of their work, the authors point out that the experimental findings indicate that the essential value of sodium sulphacetamide is likely to be prophylactic rather than curative. These experiments also emphasise the importance of early and adequate treatment (especially during the first 48 hours) in the clinical use of these drugs. One of their most important applications is likely to be in the first aid treatment of industrial injuries of the cornea, where abrasions, in the absence of effective prophylaxis, are liable to develop into septic and destructive lesions.

[A preliminary clinical report of the prophylactic use of sodium sulphacetamide solution in traumatic ulcer of the cornea in coal miners has now been published (Dickson, 1942).]

REFERENCE

Dickson, R. M. (1942), *Brit. J. Ophthal.*, **26**, 529

54

STERILIZATION OF SULPHANILAMIDE POWDER

Medical Research Council, *British Medical Journal*, **1**, 263, 27/2/43

A report (*Lancet*, 1942) of a fatal case of tetanus, possibly due to infection from local application of sulphanilamide powder, emphasises the desirability that sulphonamides and their containers for local use should be sterile. It has been shown in animals (Welch, Slocum & Herwick, 1942) that when sulphanilamide powder contaminated with tetanus spores is implanted in the tissues the development of tetanus is not prevented. At a conference held between representatives of the *Medical Research Council* and the *Association of British Chemical Manufacturers* it was agreed that a large-scale method of sterilization of sulphanilamide powder as used by Hynson, Westcott and Dunning in the U.S.A. was suitable for adoption by British manufacturers.

For small-scale sterilization of existing stocks in hospitals and elsewhere, the conference recommended the following alternative procedures:

* [The bacteriostatic substance from *Penicillium notatum* discovered as the result of the early investigations of Professor A. Fleming in London and the subsequent work of Professor H. W. Florey and his co-workers at Oxford.]

1. Dry heat maintained at 150° C. for one hour in a paraffin bath, with the technique proposed by Berry (1942) as follows: "Use dry sterile cotton-wool-plugged test-tubes [about 12 × 2 cm. or smaller]. Half fill them with the dry powdered substance, using a powder funnel. Flame the upper portion of the tubes and replug with the sterile plugs. Immerse to within one inch of the tops of the tubes in a liquid paraffin oil bath and maintain at 150° C. for one hour. If the tubes are to be stored the plugs should be covered with cellophane or paper."
2. Dry heat maintained at 150° C. for one hour in an electric oven, with precautions to ensure even heating throughout.
3. Autoclaving in a dressing sterilizer by the technique and with the precautions proposed by Buckland (1942) as follows: "An autoclave with vacuum drying attachment (dressing sterilizer) is used and the container is a dry boiling-tube plugged with non-absorbent wool. The boiling-tube must be thoroughly dried, if possible in a hot-air oven. (1) The jacket pressure of the sterilizer should be ready at a pressure of 20 to 30 lb. per square inch [about 1·4 to 2 kg. per cm.^{2}]. (2) Allow steam at 20 lb. into the empty closed chamber of the autoclave and leave for five minutes. (3) Using the appropriate valves clear chamber of all steam and condensed water. This process has heated the chamber, and the boiling-tubes, loosely plugged with non-absorbent wool and containing the powder (in 5- or 10-g. batches), are now placed in it. They should be placed on their sides, with the powder spread over their full length, giving a thinner mass for the steam to penetrate. (4) Leave the tubes for 15 minutes in the hot chamber; this heats tubes and contents sufficiently to prevent condensation inside and on the powder. (5) Autoclave at 15 lb. for half an hour. (6) Clear the chamber of steam and any condensed water quickly, and allow vacuum of 10 to 15 inches (25–37 cm.) for 15 minutes. (7) Remove tubes from autoclave, place a tight sterile plug of non-absorbent wool on the top of the one already in, and cap tubes with a suitable paper—preferably cellophane. Caking does not occur. If apparent caking is observed, it is only present while the powder is still hot and, when cool, a tap on the side of the tube is all that is necessary to show the sterile preparation to be the desired soft powder."

A proviso should be added with each of these recommendations that a sulphanilamide powder, to be satisfactory for local application, should not cake or be more than slightly discoloured with any of the techniques proposed.

The recommendations of the conference related only to sulphanilamide powder, as the sulphonamide preparation most frequently applied locally. It may be mentioned, however, that the paraffin bath technique described by Berry is recommended by the author as being suitable also for the sterilization of sulphathiazole powder in hospital practice.

References

Berry, H. (1942), *Pharm. J.*, **2**, 139
Buckland, W. J. (1942), *Brit. med. J.*, **2**, 264
Lancet (1942), **1**, 770
Welch, H., Slocum, G., & Herwick, R. P. (1942), *J. amer. med. Ass.*, **120**, 361

55

EPILEPSY FOLLOWING APPLICATION OF SULPHATHIAZOLE NEAR THE BRAIN

by A. C. Watt and G. L. Alexander, *Lancet*, **1**, 493–495, 25/4/42

This paper comes from the *Brain Injuries Unit* and the *Wilkie Surgical Research Laboratory* at Edinburgh. The local application to the brain of powdered sulphonamides has been widely adopted in neuro-surgical practice as a prophylactic against infection. Among the sulphonamides used for this purpose by the present authors was powdered sulphathiazole, but it was found that a high proportion of patients developed epileptic fits and even status epilepticus from 2 to 6 hours after operation. In all cases which developed epilepsy the dura mater had been opened and the sulphathiazole had been applied in the frontal region. Experimental application of 0·14–0·23 g. sulphathiazole powder to the fronto-temporal area of the brains of cats (of 1·6–2·5 kg. weight) under intratracheal ether anæsthesia caused epileptic attacks in 3 out of 4 animals. Epileptiform attacks were also caused by application of sulphathiazole to the occipito-temporal region in 2 cats and to the lower surface of the frontal lobe in a further 2 animals. In 2 dogs the drug was applied in the middle fossa as far medially as the carotid artery and pituitary, and severe epileptic fits were evoked. Control experiments with sulphapyridine, sulphadiazine and sulphacetamide did not result in the production of fits. It was not thought necessary to perform similar experiments with sulphanilamide in view of the published findings of Russell & Falconer (1940) and Botterell, Carmichael & Cone (1941).

Application of sulphathiazole in the region of the posterior fossa caused a "cerebellar syndrome" in 3 cats tested, while comparable experiments with sulphapyridine in 2 cats were negative. The authors conclude that sulphathiazole should not be used locally in cranial operations. The epileptogenic properties of this compound do not appear to be shared by sulphanilamide, sulphapyridine, sulphadiazine or sulphacetamide.

[Confirmation of these observations has now come from the U.S.A. and it is evident that it is dangerous to apply sulphathiazole either on or near the brain.]

References

Botterell, E. H., Carmichael, E. A., & Cone, W. V. (1941), *J. Neurol. Psychiat.*, **4**, 163
Russell, D., & Falconer, M. A. (1940), *Lancet*, **2**, 100
[*Abstracts of the above papers are available on request.*]

56

THE PRESENT STATUS OF AMINOACRIDINE COMPOUNDS (FLAVINES) AS SURFACE ANTISEPTICS

by C. H. Browning, *British Medical Journal*, **1**, 341–343, 20/3/43

The war has given a tremendous impetus to the study of antiseptic control of wound infections. One of the interesting features of recent work by British investigators is the revival of interest in the aminoacridine compounds, of which acriflavine and its precursor proflavine (salt of 2:8-diaminoacridine) were introduced as surface antiseptics by the author of the present paper and his co-workers in 1917. This paper is a review, in the light of recent experience of the properties of the diaminoacridine antiseptics, by one who has for many years been an advocate of their use. An important characteristic of these compounds is that their action is intensified rather than reduced when the medium contains a high concentration (above 10 %) of serum. Another point of importance is that they are fixed by fabrics, and application on cotton dressings therefore results in a lowered concentration of the compounds at the site of action.

The systemic toxicity of proflavine is very low—a subcutaneous dosage of 0·2 g. per kg. body weight is required to kill 50 % of mice within 2–3 days. The equi-toxic dosage of acriflavine is 0·05 g. per kg. The results in man indicate that toxic effects of absorption from locally applied proflavine or acriflavine in the amounts normally used are not to be expected. Only very slight irritation of the rabbit's cornea is produced by 3 minutes' contact with 2 % proflavine solution or 0·6 % acriflavine, but the latter compound, like most other antiseptics, was found by Russell & Falconer (1940–41) to cause hæmorrhage and necrosis of cerebral tissue in 0·1 % dilution. Proflavine in 0·1 % isotonic solution buffered at a *p*H of 6·2 was practically harmless when applied to the exposed brain.

The evidence of different investigators as to the effect of diaminoacridines on leucocytes is discordant, and the author concludes that the results *in vitro* have been determined largely by the methods used by individual workers. There are also great discrepancies in tissue-culture investigations on the effect of flavines on cells.

A useful method of testing experimentally the value of drugs in the prophylaxis of wound infection is by treating recent wounds in guinea-pigs which have been inoculated with virulent *B. diphtheriae*. Brief washing of the wound with acriflavine solution (1 % to 0·04 %) 1–2 hours after inoculation regularly saved the animals' lives, while washing with saline solution, 1 % to 5 % phenol, and "bipp" (bismuth subnitrate 25, iodoform 50, liquid paraffin 25) usually failed. Recent wounds of mice inoculated with streptococci may also

be successfully treated with aminoacridine compounds. McIntosh & Selbie (1942) found that a well-tolerated dose (0·5 mg.) of proflavine injected locally was rather more effective than 80 times the weights of sulphanilamide or sulphathiazole in preventing death in mice inoculated intramuscularly with 100 lethal doses of *Cl. welchii*. Hawking (1941) also found proflavine effective in guinea-pigs.

However, it is difficult to produce artificially in animals the suppurating wounds met with in man, and final conclusions must therefore be drawn from well-controlled clinical evidence. Recently a series of cases has been reported from the Middle East [*see BMB* **57**] in which proflavine was used with great success in the novel form of a powder in the treatment of infected wounds.

Some retardation of granulation and healing may follow continued use of the flavines, and for this reason it may be desirable to change the treatment later.

The author concludes that the supreme advantage of the flavines is their " pickling " or " cold-storage " effect, which enables wounded men to be transported without changes of dressing with the reasonable probability that their wounds will remain *in statu quo ante* as regards infection.

References

Browning, C. H., Gulbransen, R., Kennaway, E. L., & Thornton, L. H. D. (1917), *Brit. med. J.*, **1**, 73

Browning, C. H., Gulbransen, R., & Thornton, L. H. D. (1917), *Brit. med. J.*, **2**, 70

Hawking, F. (1941), *Brit. med. J.*, **1**, 263

McIntosh, J., & Selbie, F. R. (1942), *Lancet*, **2**, 750

Russell, D., & Falconer, M. A. (1940–41), *Brit. J. Surg.*, **28**, 472

57

PROFLAVINE POWDER IN WOUND THERAPY

by G. A. G. Mitchell and G. A. H. Buttle, *Lancet*, **2**, 416–419, 10/10/42

In this paper two medical officers serving with the British Army in the Middle East report a clinical experiment on the treatment of wounds with proflavine (2:8-diaminoacridine sulphate) applied locally as a powder. Sulphonamide compounds have been extensively employed in the present war and have proved effective in preventing, controlling and eliminating streptococcal wound infections, but they have proved much less effective when organisms other than streptococci were present. Wounds of bone and joints infected with staphylococci, or mixed cultures of streptococci, staphylococci, and other organisms were often particularly intractable. As proflavine was known to be a powerful and relatively non-toxic bactericide it was decided to try this antiseptic in the treatment of such cases. Eighty patients were so treated, with encouraging results in almost every case.

After preliminary cleansing of the wound, the proflavine was applied directly in the form of powder. It was dusted over the entire raw area, and introduced into cavities by means of a small Volkmann's spoon or blunt dissector. The average amount used was 0·5 g., but less was sufficient for small wounds and the maximum amount employed at any one application was 2 g. The method was often combined with the closed plaster technique, and in cases where the wound was not so covered, dressings were performed every 4–7 days.

Proflavine applied in this highly concentrated form appeared to be active against all the ordinary pyogenic organisms, except *B. proteus* and *B. pyocyaneus*. Where staphylococci were present it proved more effective in controlling or eliminating the infection than any other available drug. The effect in drying up chronically discharging wounds was sometimes remarkable, and with one doubtful exception there was no evidence of delayed healing in any case. The authors do not recommend that proflavine should supplant sulphonamides as the routine prophylactic and therapeutic agents against infection, but they believe that it is well worthy of trial in cases where these drugs have failed, and especially if the infection is staphylococcal. A mixture of 2–5 g. sulphanilamide and 0·5 g. proflavine powder was used successfully as a local wound prophylactic, and the rationale of this combined treatment was that sulphanilamide would combat streptococci while the proflavine would destroy staphylococci.

Most patients found that proflavine powder used as a dressing was unirritating. A few complained of a slight burning or tingling which rapidly abated. No general toxic manifestations, such as skin eruptions, albuminuria, jaundice, nausea, vomiting, or headache were encountered.

In discussing the significance of their results the authors comment that acriflavine has always been the most commonly used member of the acridine groups of antiseptics in spite of the experimental evidence (Albert, Francis, Garrod & Linnell, 1938 ; Falconer, 1940 ; Manifold, 1941 ; Russell & Falconer, 1940–41) that proflavine is as effective and less toxic. It has also been shown that 2:7-diaminoacridine is even less toxic than proflavine, but the former compound was not available for clinical trial by the present authors.

References

Albert, A., Francis, A. E., Garrod, L. P., & Linnell, W. H. (1938), *Brit. J. exp. Path.*, **19**, 41

Falconer, M. A. (1940), *Brit. med. J.*, **1**, 631

Manifold, M. C. (1941), *Brit. J. exp. Path.*, **22**, 111

Russell, D. S., & Falconer, M. A. (1940–41), *Brit. J. Surg.*, **28**, 472

58

I. PROPAMIDINE IN CHRONIC WOUND SEPSIS: An Experimental and Clinical Study

by W. R. Thrower and F. C. O. Valentine, *Lancet*, **1**, 133, 30/1/43

II. PROPAMIDINE IN CHRONIC STREPTOCOCCAL INFECTION OF RAW SURFACES

by A. H. McIndoe and A. R. Tilley, *Lancet*, **1**, 136, 30/1/43

III. PROPAMIDINE IN BURNS

by G. H. Mosley and J. P. Bentley, *Lancet*, **1**, 138, 30/1/43

IV. PROPAMIDINE AT AN E.M.S. HOSPITAL

by F. Kohn, M. H. Hall, and C. D. Cross, *Lancet*, **1**, 140, 30/1/43

[The therapeutic properties of the diamidine compounds were discovered by King, Lourie & Yorke (1937). They reinvestigated and confirmed the claim that " Synthalin " was trypanocidal, but found that its action was direct and was not due to a hypoglycæmic effect, as had been suggested by Jancsó & Jancsó (1935) and others. Compounds related to synthalin were then prepared and tested for trypanocidal activity. Amongst these were some diamidines, which were shown to be very active. Aromatic diamidines, prepared in the research laboratories of *May and Baker, Ltd.* (Ashley, Barber, Ewins, Newbery & Self, 1942), were found to be effective in trypanosomiasis and in other protozoal diseases, such as leishmaniasis and babesiasis.

The anti-bacterial properties of the aromatic diamidines were then investigated and as a result propamidine (4 : 4′ diamidino diphenoxypropane) was tried in *Staphylococcus aureus* septicæmia. Treatment with this substance reduced the colony counts in blood cultures but did not cure the septicæmia. Meanwhile, it had been demonstrated that the action of the diamidines, unlike that of the sulphonamides, was not inhibited by para-amino-benzoic acid or by pus and tissue fluids, and that they did not adversely affect the activity of leucocytes. Consequently propamidine was tried in the local treatment of wound sepsis and burns.]

I. *Propamidine in Chronic Wound Sepsis*

The investigation of the anti-bacterial properties of propamidine and its use in the local treatment of chronic wound sepsis are described in this paper by W. R. Thrower, consulting physician to *May and Baker, Ltd.*, and F. C. O. Valentine, director of the Inoculation Department of the *London Hospital* and pathologist in the *Emergency Medical Service* (Ministry of Health).

Two methods were employed for determining the *in vitro* activity of the substance on several strains of *Staph. aureus* and a hæmolytic streptococcus : (i) the slide-cell * technique

[* The slide-cell technique was originally described by Sir Almroth Wright (1923). In this method, 2 microscope slides are separated by 5 narrow strips of vaselined paper arranged at intervals transversely to the long axis of the slides. By this means, the space between the slides is divided into 4 very thin " cells " or compartments, each of which has a capacity of rather more than 50 mm³. Cultures in blood or other fluid media can be incubated in these cells and the effects of bacteriostatic or bactericidal substances can be studied.]

which enabled a comparison of the efficacy of propamidine and sulphathiazole to be made, and (ii) a dilutional method in broth. The lowest concentration of propamidine inhibiting the growth of staphylococci with the slide-cell method varied, with different strains, from 1 : 128,000 to 1 : 16,000. Against 3 of the 5 strains, propamidine was more effective than sulphathiazole. Para-aminobenzoic acid, in concentrations which completely inhibited the action of sulphathiazole, had no effect on the anti-bacterial action of propamidine. With the dilutional method, slightly lower concentrations of the substance were found to be effective, as compared with the slide-cell technique. The minimal effective concentration for the bactericidal effect of propamidine did not differ significantly from that for bacteriostatic action.

Repeated *in vitro* tests of the effect of propamidine on the phagocytic activity of leucocytes showed that in a concentration of 0·1%, phagocytosis was practically unaffected, 0·2% reduced it slightly and 0·4% was inhibitory, but did not kill the leucocytes. There was no hæmolysis with concentrations up to 0·4%.

Further *in vitro* tests were made to determine the effect of pus on the anti-bacterial activity of propamidine. With pus containing large numbers of staphylococci, the lowest concentration to show a bactericidal effect was 0·025%, though when fewer organisms were present 0·006% was bactericidal. With pus containing hæmolytic streptococci, the lowest bactericidal concentrations, in two experiments, were 0·003% and 0·004%. It was concluded from these experiments that a concentration of 0·1% propamidine should have little effect on the activity of leucocytes in a wound, whereas 0·025% should have considerable sterilising power.

For clinical use propamidine was incorporated in a concentration of 0·1% into a watery methyl cellulose gel of strength 4·5 to 5%. The wound was cleansed with normal saline and the cavity was filled with the jelly to skin level, using a sterile spatula. No jelly was allowed to remain on the skin edges, as long contact tends to cause inflammation. The wound and surrounding skin were then covered with two or three layers of impermeable vaseline gauze and a thin layer of gauze or wool. On re-dressing, exudate and jelly were washed out with saline and fresh jelly was applied. Satisfactory results were sometimes obtained when dressings were carried out weekly, but usually they were repeated on alternate days, or even daily if there was much discharge.

About 50 patients have been treated by this method. The results show that full benefit is obtained in 10 days. In many cases the wound had been infected for months but there was rapid improvement after application of propamidine jelly. Concentrations of more than 0·1% proved unnecessary and tended to injure granulations. Cultures from the wounds indicated that the streptococcus was the first organism to disappear, followed by the staphylococcus. If bone infection or a sequestrum is present, sinuses may persist even though the surrounding tissues become healthy. After the dangerous organisms have been removed by the application of propamidine jelly, the final closure of the wound must be brought about by skin grafting or secondary excision, though spontaneous healing may sometimes take place.

II. *Propamidine in Chronic Streptococcal Infection of Raw Surfaces*

The authors investigated the value of propamidine in clearing up persistent secondary infection by a beta-hæmolytic streptococcus of open wounds or old burns in 11 cases at the *Queen Victoria Plastic and Jaw Injury Centre*, East Grinstead. The wounds were all granulating areas with loss of skin, in which healing was retarded or grafting made difficult by persistent streptococcal infection on the surface. The propamidine was applied in the jelly form in 0·1% concentration, and was renewed every 48 hours. Swabs were taken before, during and after 10 days' treatment. Three successive negative swabs were required before an area was considered free from streptococci.

In some cases striking clinical improvement took place in the wounds within 48 hours of starting treatment with propamidine, especially in recently infected cases. From 2 to 10 days were required for control of the streptococcal infection and steady improvement occurred during this time in all cases. Occasionally reinfection took place and a second course of propamidine was required. In one case in which more than 10 days' treatment was given mild irritation of the skin took place. The authors believe that the water-soluble jelly used may not be the best vehicle for propamidine, and investigations are now being made with a different base.

III. *Propamidine in Burns*

The authors of this paper have investigated the control of established sepsis in wounds and burns and the prevention of sepsis in fresh burns at the Burns Centre of a Royal Air Force General Hospital. Seven recent burns were treated from the start with propamidine, 5 cases had received other treatment for 3 days or more and 2 cases were treated in order to prepare infected areas for skin-grafting.

Fresh burns were cleansed with saline, and dead skin was removed. A preparation containing 0·1% propamidine in a "lanette" wax (partially phosphated stearyl and cetyl alcohol) base was then spread thickly over the burned areas and a sealing dressing of vaseline gauze was applied and held in place with bandages. At 48-hour intervals the dressing was changed in a saline bath. After 10 days, treatment was changed to sulphanilamide and tulle gras dressings, to avoid the possibility of necrosis of the granulations from prolonged contact with the propamidine preparation. For infected burns, 0·05% propamidine in a water-soluble jelly base was used, as this allowed better mixing of the drug with sloughs and granulations, though it was sometimes slightly painful. The authors believe that propamidine in the form of a 0·1% concentration in lanette wax base with 1% stovaine may prove to be an almost ideal first-aid preparation for burns. This cream is simple to apply and very soothing.

In burns treated with propamidine, separation of sloughs and epithelialisation were rapid, and this, together with the mobility of the affected part during treatment, led to a minimum of scar tissue and a very good cosmetic and functional result. In some cases, the infecting organisms had become resistant to sulphonamides but yielded promptly to propamidine. Streptococcal and staphylococcal infections were effectively controlled by propamidine, but *B. proteus* and *Ps. pyocyanea* were still present in cultures after treatment. Before grafting can be carried out these organisms must be eradicated by other methods. Propamidine should not be applied for more than 10 days at a time, but a course can be repeated, if necessary, after a period of other treatment.

IV. *Propamidine at an E.M.S. Hospital*

An account of the use of propamidine in 13 cases at an *Emergency Medical Service* hospital is given by the authors of this paper. Infected wounds were cleansed with saline and the discharge was examined bacteriologically. The surrounding skin was then dried and propamidine jelly was applied to the whole surface. In some cases of burns the compound was used in a lanette wax base. The whole wound was covered with vaseline gauze and then a thin layer of cotton-wool and a bandage. Wounds were re-dressed every 48 hours and not more than 5 times in any one course of treatment. Exudate from the wound was examined bacteriologically before each dressing. In burns no preliminary cleansing was carried out, except that any coagulum due to previous tannic acid treatment was removed with the patient under general anæsthesia. The propamidine jelly or lanette wax preparation was simply applied to the burned area. No debris was removed and no blisters were opened. Active movements were encouraged from the beginning.

The results obtained in these cases were very encouraging. Thiersch or pedicle grafting was possible much earlier than with any other previous method of treatment. In wounds where skin-grafting was unnecessary, the relative freedom from infecting organisms allowed much more rapid epithelialisation than usual. In burns, pain was diminished and where there was only blistering, healing was often complete in only ten days. In no case treated immediately with propamidine did infection take place. Separation of sloughs from wounds or burns did not seem to be more rapid than usual but scar formation was not increased.

References

Ashley, J. N., Barber, H. J., Ewins, A. J., Newbery G., & Self, A. D. M. (1942), *J. chem. Soc.*, 103

Jancsó, N. von & Janscó, H. von (1935), *Z. Immunitätsforsch.*, **86**, 1

King, H., Lourie, E. M., & Yorke, W. (1937), *Lancet*, **2**, 1360

Wright, A. (1923), *Lancet*, **1**, 365, 417 & 473

59

TREATMENT OF SUPERFICIAL TUBERCULOUS LESIONS BY LOCAL APPLICATION OF PROMIN

by W. H. Tytler and A. D. Lapp, *British Medical Journal*, **2**, 748–749, 26/12/42

Experiments by the first of these authors, who is David Davies Professor of Tuberculosis in the *Welsh National School of Medicine*, had indicated that di-dextrose-sulphonate of diaminodiphenylsulphone (known as " promin " in the U.S.A., and to be known as " promanide " in Britain) had a decided inhibitory effect on the evolution of experimental tuberculosis in the guinea-pig, as reported by Feldman, Hinshaw & Moses (1940, 1941, 1942). Although the drug, administered internally, has given disappointing results in the treatment of human pulmonary tuberculosis, it was thought that it might usefully be applied locally to superficial tuberculous lesions, in which a sufficient concentration could be maintained without producing a toxic blood level and a resultant anæmia.

To reduce the rate of removal by absorption of the highly soluble drug, it was incorporated in a tragacanth jelly, of such stiffness that it could just be forced through a medium bore needle (18 SWG). Solutions containing 3·0% and 3·5% tragacanth were of suitable consistency. Varying concentrations of promin were tried and 5% was finally adopted. The jelly was applied to closed abscesses by injection, after aspiration of pus. Aspiration and injection of promin jelly were repeated when necessary. The jelly was applied to open sinuses by a fine catheter tied to the syringe, and the application was usually repeated daily.

The authors give details of 10 cases thus treated, of which 5 were closed abscesses and 5 sinuses (4 related to spinal caries and 1 to tuberculous peritonitis). In one patient three separate subcutaneous abscesses each healed completely within two weeks from the first injection. Other results were less striking but in general were considered as more favourable than might have been expected from orthodox methods. Abscesses remained flat after one or more treatments, or healed leaving fibrous residues. Sinuses decreased steadily in depth, and some were almost healed after two to four months' treatment.

The authors feel that the results justify more extensive trials, and they hope, in particular, to be able to develop this method for the treatment in the dispensary of tuberculous cervical adenitis with abscess formation, and thus to obviate the need for operative treatment in hospital.

REFERENCES

Feldman, W. H., Hinshaw, H. C., & Moses, H. E. (1940), *Proc. Mayo Clin.*, **15**, 695

Feldman, W. H., Hinshaw, H. C., & Moses, H. E. (1941), *Proc. Mayo Clin.*, **16**, 187

Feldman, W. H., Hinshaw, H. C., & Moses, H. E. (1942), *Amer. Rev. Tuberc.*, **45**, 303

60

THE NATURE OF THE VALVULAR ACTION (PASSIVE OPENING) OF THE EUSTACHIAN TUBE IN RELATION TO CHANGES OF ATMOSPHERIC PRESSURE AND TO AVIATION PRESSURE DEAFNESS

by J. E. G. McGibbon, *Journal of Laryngology and Otology*, **57**, 344–350, July, 1942

Active opening of the Eustachian tube by voluntary or involuntary muscular action has been investigated and described by many writers, but *passive opening*, and thereby passive " one way only " movement of air through the tube, is so commonly accepted that its apparent simplicity has given rise to scanty accounts of its mechanism. This phenomenon, however, is the immediate cause of aviation pressure deafness (aero-otitis)—a lesion which frequently occurs during loss of height when flying owing to failure or inability to open the Eustachian tube.

It is well known that as the extra-tympanic pressure decreases during ascent in aircraft, or during decompression in a chamber, egress of air from the middle ear through a normal Eustachian tube is easy and automatic. Armstrong and Heim (1937), who published a full account of the sensations experienced by aviators during flight, state that during decompression from sea-level pressure (760 mm. Hg.) the tympanic membrane gradually bulges outwards until at a pressure corresponding to 500 feet (152 m.) altitude (745 mm. Hg.) a " click " is heard and felt in the middle ear and simultaneously the membrane is observed to snap back to its normal position as air escapes, without any muscular effort, from the tympanum along the Eustachian tube into the naso-pharyngeal cavity. This passive opening of the Eustachian tube recurs on an average at each successive decrease of extra-tympanic pressure corresponding to an ascent of 435 feet (130 m.) irrespective of the curve of atmospheric pressures, and closure takes place again almost immediately, leaving a residual intra-tympanic positive pressure of about 3·6 mm. Hg.

During loss of height in aircraft or compression in a chamber the Eustachian tube behaves in an entirely different manner, for a normal tube does *not* open passively and air does *not* enter the tympanum without the intervention of muscular action or of therapeutic inflation. Consequently an extra-tympanic positive pressure develops which pushes the tympanic membrane inwards and invaginates it around the middle ear contents. This is often but incorrectly referred to as " retraction " of the tympanic membrane. The difference between the extra- and intra-tympanic pressures depends not only upon the amount of height lost but also on the curve of atmospheric pressures, *i.e.* the altitudes at which the loss occurs. Thus with a loss of 10,000 feet (3050 m.) from 30,000 feet (9150 m.) to 20,000 feet (6100 m.) altitude a difference of pressure of 123·6 mm. Hg. is developed. Whereas with a similar loss of 10,000 feet from 12,000 feet (3660 m.) to 2000 feet (610 m.) altitude a differential pressure of 223·4 mm. Hg. is effected.

The mechanism of passive opening and closure of the Eustachian tube can be demonstrated in the following simple manner: If a piece of Paul's rubber tubing 1 inch (2·54 cm.) in diameter and 18 inches (46 cm.) in length is fitted with a rigid mouthpiece and air is blown into it, the tubal lumen becomes patent and air escapes from its distal end. Blowing causes a condensation of air at the proximal end which travels along the lumen of the tube until it is dissipated by its exit from the distal orifice. This corresponds to passive opening of the Eustachian tube during ascent in aircraft.

If suction is applied at the mouthpiece the tubing will " collapse " so that no air can enter its lumen. This phenomenon may be explained by consideration of a rigid-walled tube with a constantly patent lumen. Suction at the proximal end of such a tube produces a rarefaction of air which progresses distally along the lumen, and until this rarefaction reaches the distal opening no air moves into the tube. There is thus a definite time-lag between suction at the proximal end and movement of air into the distal end. If rarefaction of air is produced by suction at the proximal end of a soft-walled tube its walls are immediately *pressed* together by the extra-tubal atmospheric pressure, as owing to the time-lag rarefaction is more rapidly neutralised in this manner than by movements of air into the distal end of the lumen. This closure is complete and it corresponds to the passive closure of the Eustachian tube which takes place during loss of height in aircraft.

By the use of a simple apparatus (illustrated in the original paper) which represents a tympanic cavity and Eustachian tube made to scale, the effect of atmospheric pressure changes may be demonstrated in a striking manner.

On decompression (ascent) the artificial tympanic membrane, which is made of thin glove rubber, gradually bulges outwards and then quickly returns to its normal position as air is obviously expelled through the artificial Eustachian tube. This sequence of movements of the " membrane " recurs at regular intervals and gives the impression of rhythmic pulsations.

During compression (descent) the tympanic portion of the " cartilaginous " segment (in the model, this portion is lined with lint) of the Eustachian tube becomes flattened and no air enters its lumen. The artificial drumhead is gradually pushed in until the invagination becomes so extreme that the stretched rubber almost obliterates the model middle-ear cavity, and this persists after ground-level pressure is reached.

These experiments with the model ear show that the initial changes which occur in the true middle-ear cleft as a result of variations of the atmospheric pressure may be purely mechanical and in no way physiological, and that the immediate cause therefore of the syndrome of aviation pressure deafness may also be purely mechanical. In some subjects the existence of an anatomical peculiarity or of some adjacent pathological condition may be a contributory

factor. The experiments explain also the common radiological finding in such cases of obstruction beginning in the tympanic half of the cartilaginous Eustachian tube.

Armstrong & Heim state that at an extra-tympanic positive pressure of 90 mm. Hg. or more the Eustachian tube "locks," as the muscles concerned with its opening are unable to overcome this force. The necessity of actively opening the tube or of auto-inflation during loss of height in aircraft to avoid this "locking" is generally recognised and practised by flying personnel. If, however, these methods are not adopted or fail, "forced ventilation" of the middle ear by Politzer's bag or by Eustachian catheterisation will frequently be successful. Forced ventilation of this type can take place only because the ostium of the tube, although varying in shape, is formed anatomically as an open funnel. If there were a true valve at the orifice, increased naso-pharyngeal pressure would merely augment the degree of closure.

Decompression in a chamber or ascent in aircraft if carried out early may also relieve the symptoms, as by these means the extra- and intra-tympanic pressures are equalised. If these latter therapeutic measures are employed re-compression or descent must be carried out cautiously and the tube must be actively and regularly opened throughout the period of increase of atmospheric pressure.

In conclusion, the author emphasises the advisability of early treatment, because experience has shown that the severity of the effects of decreased intra-tympanic pressures, which have been aptly compared to dry-cupping of the tympanic mucosa, is aggravated by the lapse of time.

REFERENCE

Armstrong, H. G., & Heim, J. W. (1937), *J. amer. med. Ass.*, **109**, 417

61

THE TREATMENT OF THE INJURED WORKMAN

by W. Gissane, *Practitioner*, **149**, 349–353, December, 1942

This paper deals with the social aspects of the subject rather than with technical procedures. The author is one of the leading British authorities on the rehabilitation of the injured industrial worker, and is Surgeon-in-Chief and Clinical Director of the *Birmingham Accident Hospital* and *Rehabilitation Centre*.

It is becoming generally recognised that the treatment of the injured workman is a social as well as a surgical process. Personal feelings, above all the will of the workman to get well, play a decisive part in treatment, and the retention of this spirit throughout the whole period of treatment is of primary concern to any organisation set up to treat the injured workman. The principles for efficient treatment were laid down by Sir Robert Jones at the end of the last war.

A special committee of the British Medical Association in 1935 and an Interdepartmental Committee of the Home Office and the Ministry of Health in 1939 unanimously advocated the following measures:

1. Segregation of patients to special treatment centres.
2. Unity of control throughout treatment by the same surgical team.
3. Careful after-care.
4. Rehabilitation.

The most economic method of treating the injured workman is to give the most thorough surgical treatment possible from the stage of first aid right through to the workman's discharge from hospital. Further, hospital treatment must be actively concerned with the process of rehabilitation, or reconditioning: that is, the process of preventing or restoring the loss of muscle tone, restoring full function of the limbs and maintaining the patient's general health and mental alertness, in addition to the surgical treatment of the injured part. At the end of properly planned hospital treatment, which includes rehabilitation within the hospital, the majority of injured workmen (about 80 %) are capable of returning immediately to their pre-accident job. For the remaining 20 % of injured workmen, who, owing to the severity of the accident or to their resistance to treatment, are incapable of returning immediately to their pre-accident job, special Centres away from the hospital are being used in Britain. In these Centres, treatment is concentrated purely on reconditioning weak muscles and building up general bodily strength and mental alertness. The workmen are resident in the Centres, and their work is gradually increased until they are capable of doing a full day's work.

For many workmen with the less severe type of fracture of the limbs who have to spend some period in plaster casts and yet are capable of walking and doing some work, workshops are being provided within the factory where the men are usefully employed under medical supervision. These sheltered workshops not only provide the workmen with facilities for earning money to supplement their compensation pay, but they are also used at the end of hospital treatment to up-grade some injured workmen gradually until they reach their pre-accident state.

Since the war there has been an increase in the number of factory accidents, and the full treatment of these workpeople has become a problem of national importance. The increase of reportable factory accidents in 1941 over those of the pre-war year of 1938 is as follows: Adult males, 42 %. Adult females, 192 %.

Finally, to ensure provision for those whose injury has resulted in such permanent disability that they are not physically capable of following their trade, there are *Vocational Retraining Centres*, and in one such Centre 500 trainees have been returned to industry since 1935 and, in spite of grave physical disability, have been found capable of competing in certain types of work on equal terms with the able-bodied.

62

BAGASSOSIS. AN INDUSTRIAL LUNG DISEASE

by L. I. M. Castleden and J. L. Hamilton-Paterson, *British Medical Journal*, **2**, 478–480, 24/10/42

Sugar cane from which sugar has been removed is called bagasse. It consists of fibre with 1 % protein and 5–7 % silica. Board is made from bagasse by crushing it into small fragments either under water or dry. After crushing the material is washed and remains wet until the finished board is dried in a press at 200° F. (93° C.). The dry board is then sawn and trimmed. Dust is present in the air of the factory (1) where the bagasse is crushed, (2) at the sawmill, where it differs from that liberated at (1) in containing no protein. Since the dry crushing process was begun cases of lung disease have occurred among the workers feeding the crushing machine.

Case 1

A labourer aged 19 began a cough with increasing shortness of breath after two months' exposure to bagasse dust. His previous health had been very good. On admission to hospital six weeks after his illness began he was extremely short of breath, cyanosed, and had the signs of bronchopneumonia in both lungs. Examination was otherwise normal. Sputum was scanty, viscid and sometimes blood-stained with no pathogenic organisms in it. The blood count was normal. X-ray confirmed the presence of a bronchopneumonic type of lung lesion. The disease did not respond to sulphapyridine but oxygen relieved his dyspnœa. There was a rise of temperature on a few days only in the course of an illness which lasted 7½ weeks and ended by gradual disappearance of dyspnœa with accompanying clinical and radiological signs of resolution. He eventually returned to normal health with complete resolution of the lung lesions radiologically.

Case 2

An engineer aged 31 whose health had been good had an acute illness described as pneumonia after six months' exposure to the dust. He recovered from this illness (which was similar to that of Case 1) after 10 weeks and returned to work. Two months after resuming work he began to have increasing shortness of breath. When he attended as an out-patient he had a kyphotic emphysematous chest with clubbing of the fingers and fine râles in both lungs. An X-ray showed a few apical scars and a little fibrosis in the right mid-zone. Five months later his shortness of breath was extreme. He would now collapse from the slightest exertion and was admitted to hospital.

On examination there was marked dyspnœa at rest with orthopnœa but no cyanosis. Clubbing of the fingers was now more definite. The chest was kyphotic and rigid, with

signs of consolidation at the left apex and râles throughout the left lung and at the right base. Physical examination was otherwise normal. A blood count showed an eosinophilia of 1122 per mm³. but was otherwise normal. Sputum was viscid, mucoid, scanty, never bloodstained and contained no pathogenic organisms, yeasts or fungi. He was afebrile throughout his stay of 3 months in hospital during which time his shortness of breath decreased until he was able to be out of bed without distress. X-ray shortly after admission showed wide upper mediastinal shadow, irregularity of contour of right diaphragm with pleural thickening in the costophrenic angle and streaky opacities of fibrotic appearance in both lungs. He has continued to attend as an out-patient with further symptomatic improvement but with no change in either the physical signs or radiological appearances.

Case 3

A labourer aged 40 had cough and shortness of breath after one month's exposure to the dust. After transfer to another part of the factory his symptoms had improved.

On examination he was a little short of breath. The chest movements were poor with impairment of percussion note and diminished breath sounds at the left base. There were no adventitious sounds and an X-ray showed no lung lesion. A blood count was normal.

Case 4

A labourer aged 44 had increasing shortness of breath and a cough after 4 months' exposure to the dust. He was transferred to outdoor work with improvement of his symptoms. On examination there was moderate cyanosis with dyspnœa at rest. The chest showed an impaired percussion note at the right apex with diminished breath sounds and rhonchi throughout all areas of both lungs. Physical examination was otherwise normal. A blood count was normal. An X-ray showed a general streaky opacity throughout both lungs.

The clinical appearance of these patients suggested an acute inflammatory lung disease with urgent and extreme dyspnœa but little or no febrile reaction. Case 1 appeared to be a bronchopneumonia of unknown ætiology. Case 2 seemed to be suffering from pulmonary tuberculosis though this could not be proved. The common factor of the inhalation of bagasse dust led to further enquiry and it was found that a case similar in all respects to Case 1 had been described by Jamison & Hopkins (1941). These writers were able to grow a fungus from the sputum of their case which, like Case 1, recovered completely.

It appears that bagasse dust is capable of causing a pathological process in the lungs which may either resolve completely as in Cases 1 and 3 or progress to a fibrotic lesion as in cases 2 and 4. Since no pathogenic organism or fungus could be isolated from the sputum of these cases it seemed possible that an allergic factor might play a part in the disease. Extracts for skin tests were therefore made from whole bagasse in several solvents, that finally adopted being a normal saline extract of 20 grammes of coarsely crushed bagasse in 200 ml. saline with 0·25% tricresol added. After standing for five days with occasional shaking it was filtered through a Seitz filter. A control of normal saline with 0·25% tricresol was also prepared. All the extracts gave negative results by the scratch technique, but positive results by the intradermal injection of 0·2 ml. in cases 2, 3 and 4. The saline extract gave a skin reaction which attained a maximal area of 40 mm. in 36 hours. Seventeen normal controls gave a negative reaction to this test. A similar extract from dust at the sawmill gave negative results when tested on Cases 2, 3 and 4.

The acute phase of the disease may therefore be an allergic response to this saline-soluble antigen with or without an added infective factor. The nature of the chronic process is obscure. It might be (1) silicosis, (2) due to cellulose, (3) fibrosis occurring in tissues œdematous from the allergic phase. No opportunities for the study of the morbid anatomy of the condition have yet occurred.

The original paper is illustrated by 8 radiographs.

REFERENCE

Jamison, S. C., & Hopkins, J. (1941), *New Orleans med. surg. J.*, **93**, 580

63

NON-GONOCOCCAL URETHRITIS

by I. N. Orpwood-Price, *British Journal of Venereal Diseases*, **18**, 112–116, July–October, 1942

This paper was read at a meeting of the Medical Society for the Study of Venereal Diseases. Figures obtained after investigation of 500 consecutive patients suffering from a urethral discharge and attending the Whitechapel and *University College* Hospital Clinics (London) show the incidence of non-gonococcal urethritis amongst the civilian population to be 20% of all urethral discharges. As 80% of urethral discharges are gonococcal in origin, the diagnosis of non-gonococcal urethritis is usually by exclusion.

Of the aids to diagnosis, serum tests are of primary importance. The Wassermann Reaction should be performed as a routine in view of the possibility of an intra-urethral chancre. The Complement Deviation Test for gonorrhœa must be done, as hidden foci of gonococcal infection are often not demonstrable by the usual smears. The author believes that a *persistently* positive reaction, even in the absence of other evidence, is a definite indication of the presence of a gonococcal infection. A diagnosis of non-gonococcal urethritis, however, cannot be made on the strength of one negative reaction, but if it is persistent and is reviewed in conjunction with the clinical picture and other pathological tests, the reaction is of real assistance.

Cultures from the anterior urethra should in the author's opinion always be made, although if gonococci are not obtained not much information can be gathered from the organisms which are grown. Of paramount importance are vesicular cultures. This short term indicates that the material inoculated is obtained from the posterior urethra, prostate gland, and seminal vesicles by so-called prostatic massage. The author describes important details of technique, including the bacteriological examination by means of the oxidase reaction.

Care must be taken that the culture medium is suitable, and failures may be due to (*a*) poor quality of meat used in the preparation of broth, (*b*) inferior preparation of peptone, (*c*) unsuitable agar.

Direct smears from the urethra and prostate often yield valuable information.

The author concludes by emphasising that it is impossible to arrive at a diagnosis of non-gonococcal urethritis until the possibility of gonorrhœa has been excluded.

Corrections to BMB No. 1

BMB 15

(*i*) *The reference to the page numbers of the original should have been 44–85,* not *44–84.*

(*ii*) *In line 5 from the bottom, 60% should be 69%.*

BMB 21

In line 12, "usually 15 to 20 grams" is misleading. Of 41 cases in the series, only 9 received 15–20 grams. In 2 cases more than this amount (25 and 40 grams) was given, while less was given in the remaining 30 cases (14 cases, 1–5 grams; 12 cases, 8–10 grams; 4 cases, 12 grams).

This Bulletin is published by the British Council. Requests for further information about any of the investigations reported should be addressed to The British Council, Medical Department, 3 Hanover Street, London, W. 1, England

Printed by Spottiswoode, Ballantyne and Co. Ltd., Colchester, London and Eton